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=> s recombinant Fel dI L1 5 RECOMBINANT FEL DI

=> dup remove l1
PROCESSING COMPLETED FOR L1
L2 2 DUP REMOVE L1 (3 DUPLICATES REMOVED)

=> d 12 1-2 cbib abs

L2 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
2000:240992 Document No. 132:264085 Recombinant cat allergen, Fel dI,
expressed in baculovirus for diagnosis and treatment of cat allergy.
Guyre, Paul M.; Goldstein, Joel J.; Wu, Zining; Sun, Wanwen (Trustees of
Dartmouth College, USA; Medarex, Inc.). PCT Int. Appl. WO 2000020032 A1
20000413, 15 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN:
PIXXD2. APPLICATION: WO 1999-US23251 19991005. PRIORITY: US 1998-103284
19981006.

AB Recombinant Fel dI cat allergens expressed in baculovirus for diagnosis and treatment of allergy to cats in humans are provided.

L2 ANSWER 2 OF 2 MEDLINE DUPLICATE 1
94049844 Document Number: 94049844. PubMed ID: 8232338. Native and
recombinant Fel dI as probes into the
relationship of allergen structure to human IgE immunoreactivity. Bond J
F; Brauer A W; Segal D B; Nault A K; Rogers B L; Kuo M C. (ImmuLogic
Pharmaceutical Corporation, Waltham, MA 02154.) MOLECULAR IMMUNOLOGY,
(1993 Nov) 30 (16) 1529-41. Journal code: 7905289. ISSN: 0161-5890. Pub.
country: ENGLAND: United Kingdom. Language: English.

AB To delineate the relationship between the structural conformation and the stability of an allergen and its antigenicity, we have chosen the major allergen from cat dander, Fel dI. From protein sequence analysis data we have examined the structure of the naturally occurring Fel dI and we have found it to exist as an anti-parallel heterodimer. We have used ELISA, RAST, Western blot and histamine release techniques to compare the IgE reactivity of a set of cat allergic patient samples to purified, native Fel dI and the E. coli expressed chains 1 and 2. Results from these studies demonstrate a significant level of IgE reactivity to all forms when examined for direct binding. However, both blot and ELISA competition assays show a much higher reactivity to Fel dI in solution compared to the

separate recombinant chains and this is supported by the histamine release data. Although native Fel dI chain 2 contains an N-linked carbohydrate moiety, this does not seem to play a role in the reactivity of IgE to chain 2. Denaturation of Fel dI with alkali conditions leads to a dramatic decrease in IgE reactivity, even though measurable changes to the backbone structure of the protein are minimal. One proposed explanation is that both chains possess a core region determined by their primary structures and that the major IgE epitopes are dependent upon them. The relative reactivity amongst these allergen forms varied with the method of analysis, implying that the conformational requirements for IgE antibody binding are best studied by the application of more than one experimental protocol. Results from these qualitative analyses afford insight into the allergenicity of this exceptionally stable cat pelt protein.

=> s recombinant cat allergen
L3 4 RECOMBINANT CAT ALLERGEN

=> dup remove 13
PROCESSING COMPLETED FOR L3
L4 4 DUP REMOVE L3 (0 DUPLICATES REMOVED)

=> d 14 1-4 cbib abs

- L4 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2002 ACS
 2000:240992 Document No. 132:264085 Recombinant cat
 allergen, Fel dI, expressed in baculovirus for diagnosis and
 treatment of cat allergy. Guyre, Paul M.; Goldstein, Joel J.; Wu, Zining;
 Sun, Wanwen (Trustees of Dartmouth College, USA; Medarex, Inc.). PCT Int.
 Appl. WO 2000020032 A1 20000413, 15 pp. DESIGNATED STATES: W: CA, JP;
 RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT,
 SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US23251 19991005.
 PRIORITY: US 1998-103284 19981006.
 AB Recombinant Fel dI cat allergens expressed in baculovirus for diagnosis
- L4 ANSWER 2 OF 4 SCISEARCH COPYRIGHT 2002 ISI (R)
 1999:143414 The Genuine Article (R) Number: 165FC. Fully immunoreactive
 recombinant CAT allergen, Fel dl, expressed in
 baculovirus.. Ichikawa K (Reprint); Sun W; Wu Z; Vailes L D; Guyre P;
 Chapman M D. DARTMOUTH COLL SCH MED, LEBANON, NH; UNIV VIRGINIA,
 CHARLOTTESVILLE, VA 22903. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN
 1999) Vol. 103, No. 1, Part 2, Supp. [S], pp. 704-704. Publisher:
 MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318

and treatment of allergy to cats in humans are provided.

. ISSN: 0091-6749. Pub. country: USA. Language: English.

- L4 ANSWER 3 OF 4 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
 1999:125631 Document No.: PREV199900125631. Fully immunoreactive

 recombinant CAT allergen, Fel d 1, expressed
 in baculovirus. Ichikawa, K. (1); Sun, W.; Wu, Z.; Vailes, L. D.; Guyre,
 P.; Chapman, M. D.. (1) Dartmouth Med. Sch., Lebanon, NH USA. Journal of
 Allergy and Clinical Immunology, (Jan., 1999) Vol. 103, No. 1 PART 2, pp.
 S184. Meeting Info.: 55th Annual Meeting of the American Academy of
 Allergy, Asthma and Immunology Orlando, Florida, USA February 26-March 3,
 1999 American Academy of Allergy, Asthma, and Immunology. ISSN: 0091-6749.
 Language: English.
- L4 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2002 ACS
 1994:52097 Document No. 120:52097 Expression of recombinant Fel d I:
 Purification, antibody binding and reaction with cat allergic human T
 cells. Rogers, Bruce L.; Garman, Richard D.; Kuo, Mei Chang; Bond, Julian
 F.; Craig, Sandra; Chen, Meei Song; Greenstein, Julia L.; Morgenstern, Jay
 P. (ImmuLogic Pharm. Corp., Cambridge, MA, 02139, USA). Mol. Biol.

Immunol. Allergens, 259-62. Editor(s): Kraft, Dietrich; Sehon, Alec H. CRC: Boca Raton, Fla. (English) 1993. CODEN: 59QMA6.

This report describes the subcloning, high level expression in E. coli, and purifn. of chain 1 and 2. Further, these recombinant polypeptides were examd. for their antibody binding capacity and ability to stimulate human cat-allergic T-cells in in vitro cultures.

=> d 19 1-4 cbib abs

L9 ANSWER 1 OF 4 MEDLINE DUPLICATE 1
2001669005 Document Number: 21571693. PubMed ID: 11714794. Receptor modulation by Fc gamma RI-specific fusion proteins is dependent on receptor number and modified by IgG. Guyre C A; Keler T; Swink S L; Vitale L A; Graziano R F; Fanger M W. (Department of Physiology, Dartmouth Medical School, Lebanon, NH 03756, USA.) JOURNAL OF IMMUNOLOGY, (2001 Dec 1) 167 (11) 6303-11. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

The high-affinity IgG receptor, FcgammaRI (CD64), is constitutively AΒ expressed exclusively on professional APCs. Human FcgammaRI binds monomeric IgG with high affinity and is, therefore, saturated in vivo. The binding of IgG to FcgammaRI causes receptor recycling, while Abs that cross-link FcgammaRI cause rapid down-modulation of surface FcgammaRI. Because studies performed in the absence of ligand may not be representative of FcgammaRI modulation in vivo, we investigated the ability of FcgammaRI-cross-linking Abs and non-cross-linking derivatives to modulate FcgammaRI in the presence and absence of ligand. In the absence of ligand mAb H22 and wH22xeGFP, an enhanced green fluorescent protein (eGFP)-labeled fusion protein of H22, cross-linked and rapidly down-modulated surface FcgammaRI on the human myeloid cell line, U937, and its high FcgammaRI-expressing subclone, 10.6. This effect was dependent on the concentration of fusion protein and the level of FcgammaRI expression and correlated with internalization of both wH22xeGFP and FcgammaRI, itself, as assessed by confocal microscopy. A single-chain Fv version, sFv22xeGFP, which does not cross-link FcgammaRI, was unable to modulate FcgammaRI in the absence of IgG. However, if ligand was present, treatment with either monovalent or cross-linking fusion protein led to intracellular receptor accumulation. These findings suggest at least two alternate mechanisms of internalization that are influenced by ligand and demonstrate the physiologic potential of FcgammaRI to transport a large antigenic load into APCs for processing. These studies may lead to the development of better FcgammaRI-targeted vaccines, as well as therapies to down-modulate FcR involved in autoimmune diseases.

L9 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2002 ACS 1998:749352 Document No. 130:24108 Therapeutic compounds comprised of

anti-Fc receptor antibodies. Deo, Yashwant M.; Goldstein, Joel; Graziano, Robert; Somasundaram, Chezian (Medarex Inc, USA). U.S. US 5837243 A 19981117, 57 pp., Cont.-in-part of U. S. Ser. No. 484,172. (English). CODEN: USXXAM. APPLICATION: US 1996-661052 19960607. PRIORITY: US 1995-484172 19950607.

- Multispecific multivalent mols. which are specific to an Fc receptor (FcR, Fc.gamma. receptor or Fc.gamma. RI) and to EGF, bombesin or carcinoembryonic antigen are described. These multivalent antibodies or humanized antibodies are useful inducing antibody—dependent cellular cytotoxicity against tumor cells such as breast cancer, sarcoma, carcinoma and ovarian cancer. Bispecific antibody comprising anti-Fc.gamma.RI (H22) and anti-HER2/neu antibodies was produced. H22-EGF fusion protein, H22-bombesin fusion protein, H22-heregulin fusion protein, and single chain bispecific anti-Fc.gamma.RI-anti-CEA mols. were prepd. for inducing antitumor cytotoxic T cells.
- L9 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2002 ACS
- 1998:687785 Document No. 130:51105 The nature of antibody heavy chain residue H6 strongly influences the stability of a VH domain lacking the disulfide bridge. Langedijk, Annette C.; Honegger, Annemarie; Maat, Jan; Planta, Rudi J.; Van Schaik, Rene C.; Pluckthun, Andreas (Biochemisches Institut Universitat Zurich, Zurich, CH-8057, Switz.). Journal of Molecular Biology, 283(1), 95-110 (English) 1998. CODEN: JMOBAK. ISSN: 0022-2836. Publisher: Academic Press.
- Monoclonal antibody mAb 03/01/01, directed against the musk AΒ odorant traseolide, carries a serine residue instead of the conserved Cys H92 in the heavy chain variable domain, and is thus lacking the highly conserved disulfide bridge. We investigated the energetic consequence of restoring the disulfide bond and the nature of residue H6 (Glu or Gln), which is poised to interact with Ser H92 in the recombinant scFv fragment obtained from this antibody. In the scFv fragment derived from this antibody, the stabilizing effect of Gln H6 over Glu was found to be as large as the effect of reintroducing the disulfide bond. We have analyzed the conformation and hydrogen bond pattern of Gln H6 and Glu H6 in antibodies carrying these residues and suggest mechanisms by which this residue could contribute to VH domain stability. We also show that the unpaired cysteine H22 is buried, and conforms to the expected VH structure. The antibody appears to have acquired two somatic mutations (Ser H52 and Arg H66), which had been previously characterized as having a pos. effect on VH stability. The overall domain stability is the decisive factor for generating functional, disulfide-free antibody domains, and several key residues play dominant roles. (c) 1998 Academic Press.
- L9 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2002 ACS
- 1997:98030 Document No. 126:170168 A natural antibody missing a cysteine in VH: consequences for thermodynamic stability and folding. Proba, Karl; Honegger, Annemarie; Plueckthun, Andreas (Biochemisches Institut, Universitaet Zurich, Zurich, CH-8057, Switz.). Journal of Molecular Biology, 265(2), 161-172 (English) 1997. CODEN: JMOBAK. ISSN: 0022-2836. Publisher: Academic.
- While the disulfide bridge is highly conserved within the Ig fold, a few antibody variable domains lack one of the essential cysteine residues. In the levan binding antibody ABPC48 one of the essential cysteine residues (Cys H92) of the heavy chain variable domain is replaced by tyrosine. The authors expressed scFv fragments with the ABPC48 sequence and a mutant in which the VH disulfide bond has been restored in Escherichia coli, purified both proteins by antigen affinity chromatog. and characterized them by equil. denaturation. While the ABPC48 protein was significantly less stable than an av. scFv mol., the restored disulfide increased its stability above that of other, unrelated

scFv fragments, explaining why it tolerates the disulfide loss. Surprisingly, the authors obsd. that under some refolding conditions, the unpaired cysteine residue of functional scFv of ABPC48 is derivatized by glutathione. It is easily accessible to other reagents and thus appears to be solvent-exposed, in contrast to the deeply buried disulfide of ordinary variable domains. This implies a very unusual conformation of strand b contg. the unpaired Cys H22, which might be stabilized by interactions with the tyrosine residue in position H92.

=> s anti-CD64 L10 97 ANTI-CD64

=> s 110 and single chain L11 2 L10 AND SINGLE CHAIN

=> dup remove 111
PROCESSING COMPLETED FOR L11
L12 2 DUP REMOVE L11 (0 DUPLICATES REMOVED)

=> d 112 1-2 cbib abs

L12 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2002 ACS
2002:262600 Review - second generation bispecific antibodies: Applications in cancer immunotherapy. Kudo, Toshio; Suzuki, Masanori; Takemura, Shin-Ichi; Asano, Ryutaro; Tumoto, Koh-hei; Katayose, Yu; Shinoda, Masao; Sakurai, Naoki; Kodama, Hideaki; Ichiyama, Masahiko; Yoshida, Hiroshi; Hayashi, Hiroki; Saijyo, Susumu; Saito, Sachiko; Takahashi, Jitsuko; Imai, Kohzoh; Kumagai, Izumi (Cell Resource Center for Biomedical Research. Institute of Development. Aging and Cancer, Tohoku University, Sendai, 980-8575, Japan). Recent Research Developments in Cancer, 3(Pt. 1), 235-255 (English) 2001. CODEN: RRDCCP. Publisher: Transworld Research

In order to enhance cell mediated cytotoxicity, bispecific AΒ antibodies (BsAbs), mols. combining two antibodies with different antiquenic specificities, have been developed as new agents for cancer immunotherapy. Our recent studies revealed that simultaneous administration of two kinds of BsAbs (anti-tumor x anti-CD3 plus anti-tumor x anti-CD28) together with lymphokine activated killer cells with a T cell phenotype (T-LAK cells) inhibited growth of human. Xenotransplanted tumors in severe combined immunodeficient (SCID) mice, while single BsAbs were without effect. The combination of three kinds of BsAbs (anti-tumor x anti-CD3, anti-tumor x anti-CD28, and anti-tumor x anti-CD2) showed the higher cytotoxicity against tumor cells when given simultaneously with T-LAK cells or peripheral blood mononuclear cells (PBMCs). Recent advances in genetic engineering have made it possible to construct recombinant BsAbs from heterogenous singlechain antibodies (scFv). The recombinant BsAb, named a diabody is one of the smallest recombinant BsAbs, and one example (anti-tumor \boldsymbol{x} anti-CD3) produced in our lab. demonstrated almost identical antitumor activity to that with the chem. produced counterpart (anti-tumor \boldsymbol{x} anti-CD3). As a second generation BsAb, SEA-D227A (mutated superantigen) was genetically fused to one of the hetero scFv of the diabody (anti-tumor x anti-CD3) and this SEA-D227A-fusion diabody demonstrated the best antitumor activity among BsAbs produced in our lab. BsAbs can be preserved for immediate application, while cytotoxic T lymphocytes (CTLs) must be made-to-order, and are time-consuming to prep. Tumor assocd. antigens, such as MAGE, SART, MUC1, c-erbB2, CEA antigens or cancer/testis antigens can be served to target antigens for BsAb prodn. By conjugation with antibodies targeting various effector cells (anti-CD3, anti-CD28, anti-CD16, anti-CD64, anti-CD89 or anti-CD2), many kinds of BsAbs can be produced to cover most types of cancers at different organ sites. Therefore this BsAb strategy might be almost ubiquitously

applicable to malignancies. second generation bispecific antibody; specific targeting immunotherapy; MUC1; SEA; diabody. L12 ANSWER 2 OF 2 SCISEARCH COPYRIGHT 2002 ISI (R) The Genuine Article (R) Number: 480UY. A single 2001:870482 chain Fv anti-CD64 : ovalbumin fusion protein augments antigen presentation and results in higher IgG2a production.. Sulahian T H (Reprint); Sun A; Symmes R E; Goldstein J; Wardwell K; Moser R; Guyre P M. Dartmouth Coll Sch Med, Dept Physiol, Lebanon, NH USA; Medarex Inc, Annandale, NJ USA. JOURNAL OF LEUKOCYTE BIOLOGY (30 OCT 2001) Supp. [S], pp. 75-75. MA 247. Publisher: FEDERATION AMER SOC EXP BIOL. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA. ISSN: 0741-5400. Pub. country: USA. Language: English. => s baculovirus 35173 BACULOVIRUS T.13 => s l13 and Fel dI 1 L13 AND FEL DI => d l14 cbib abs L14 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS Document No. 132:264085 Recombinant cat allergen, Fel 2000:240992 dI, expressed in baculovirus for diagnosis and treatment of cat allergy. Guyre, Paul M.; Goldstein, Joel J.; Wu, Zining; Sun, Wanwen (Trustees of Dartmouth College, USA; Medarex, Inc.). PCT Int. Appl. WO 2000020032 A1 20000413, 15 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US23251 19991005. PRIORITY: US 1998-103284 19981006. Recombinant Fel dI cat allergens expressed in baculovirus for diagnosis and treatment of allergy to cats in humans are provided. => s Fel dI 70 FEL DI L15 => s 115 and chain 1 31 L15 AND CHAIN 1 L16 => s 116 and chain 2 19 L16 AND CHAIN 2 L17 => s 117 and linker 0 L17 AND LINKER => s (guyre p?/au or goldstein j?/au or wu z?/au) 22423 (GUYRE P?/AU OR GOLDSTEIN J?/AU OR WU Z?/AU) T.19 => s 119 and cat allergen 3 L19 AND CAT ALLERGEN => dup remove 120 PROCESSING COMPLETED FOR L20 3 DUP REMOVE L20 (0 DUPLICATES REMOVED) => d 121 1-3 cbib abs L21 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2002 ACS

2000:240992 Document No. 132:264085 Recombinant cat

AΒ

allergen, Fel dI, expressed in baculovirus for diagnosis and treatment of cat allergy. Guyre, Paul M.; Goldstein, Joel J.; Wu, Zining; Sun, Wanwen (Trustees of Dartmouth College, USA; Medarex, Inc.). PCT Int. Appl. WO 2000020032 A1 20000413, 15 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US23251 19991005. PRIORITY: US 1998-103284 19981006.

AB Recombinant Fel dI cat allergens expressed in baculovirus for diagnosis and treatment of allergy to cats in humans are provided.

L21 ANSWER 2 OF 3 SCISEARCH COPYRIGHT 2002 ISI (R)
1999:143414 The Genuine Article (R) Number: 165FC. Fully immunoreactive recombinant CAT allergen, Fel dl, expressed in baculovirus.. Ichikawa K (Reprint); Sun W; Wu Z; Vailes L D;
Guyre P; Chapman M D. DARTMOUTH COLL SCH MED, LEBANON, NH; UNIV VIRGINIA, CHARLOTTESVILLE, VA 22903. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (JAN 1999) Vol. 103, No. 1, Part 2, Supp. [S], pp. 704-704. Publisher: MOSBY-YEAR BOOK INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318. ISSN: 0091-6749. Pub. country: USA. Language: English.

L21 ANSWER 3 OF 3 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1999:125631 Document No.: PREV199900125631. Fully immunoreactive recombinant

CAT allergen, Fel d 1, expressed in baculovirus.

Ichikawa, K. (1); Sun, W.; Wu, Z.; Vailes, L. D.; Guyre,

P.; Chapman, M. D.. (1) Dartmouth Med. Sch., Lebanon, NH USA. Journal

of Allergy and Clinical Immunology, (Jan., 1999) Vol. 103, No. 1 PART 2,

pp. S184. Meeting Info.: 55th Annual Meeting of the American Academy of

Allergy, Asthma and Immunology Orlando, Florida, USA February 26-March 3,

1999 American Academy of Allergy, Asthma, and Immunology. ISSN: 0091-6749.

Language: English.

=> s 119 and Fel dI L22 1 L19 AND FEL DI

=> d 122 cbib abs

L22 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
2000:240992 Document No. 132:264085 Recombinant cat allergen, Fel
 dI, expressed in baculovirus for diagnosis and treatment of cat
 allergy. Guyre, Paul M.; Goldstein, Joel J.; Wu,
 Zining; Sun, Wanwen (Trustees of Dartmouth College, USA; Medarex,
 Inc.). PCT Int. Appl. WO 2000020032 A1 20000413, 15 pp. DESIGNATED
 STATES: W: CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
 IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO
 1999-US23251 19991005. PRIORITY: US 1998-103284 19981006.

AB Recombinant Fel dI cat allergens expressed in
 baculovirus for diagnosis and treatment of allergy to cats in humans ar

baculovirus for diagnosis and treatment of allergy to cats in humans are provided.

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